

07-20 -00

A

07/19/00

Please type a plus sign (+) inside this box → ☐

Approved for use through 09/30/2000. OMB 0651-0032
 Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
 Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No. Knowles/Hair Loss
 First Inventor or Application Identifier Knowles
 Title Hair Loss
 Express Mail Label No. _____

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☒ * Fee Transmittal Form (e.g., PTO/SB/17)
(Submit an original and a duplicate for fee processing)
2. ☒ Specification [Total Pages 26]
(preferred arrangement set forth below)
 - Descriptive title of the invention
 - Cross References to Related Applications
 - Statement Regarding Fed sponsored R & D
 - Reference to Microfiche Appendix
 - Background of the invention
 - Brief Summary of the invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description
 - Claim(s)
 - Abstract of the Disclosure
3. ☐ Drawing(s) (35 U.S.C. 113) [Total Sheets 1]
4. Oath or Declaration [Total Pages 1]
 - a. ☒ Newly executed (original or copy)
 - b. ☐ Copy from a prior application (37 C.F.R. § 1.63(d))
(for continuation/divisional with Box 16 completed)
 - i. ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

* NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

ADDRESS TO: Assistant Commissioner for Patents
 Box Patent Application
 Washington, DC 20231

5. ☐ Microfiche Computer Program (Appendix)
6. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
 - a. ☐ Computer Readable Copy
 - b. ☐ Paper Copy (identical to computer copy)
 - c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. ☐ Assignment Papers (cover sheet & document(s))
8. ☐ 37 C.F.R. § 3.73(b) Statement of Power of Attorney (when there is an assignee)
9. ☐ English Translation Document (if applicable)
10. ☒ Information Disclosure Statement (IDS)/PTO-1449 ☒ Copies of IDS Citations
11. ☐ Preliminary Amendment
12. ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
13. ☐ * Small Entity Statement(s) filed in prior application, Status still proper and desired (PTO/SB/09-12)
14. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)
15. ☒ Other: Petition To Make Special

16. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No. _____

Prior application information: Examiner _____ Group / Art Unit: _____

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

17. CORRESPONDENCE ADDRESS

☒ Customer Number or Bar Code Label



(Insert Customer No. or Attach bar code label here)

or ☐ Correspondence address below

Name

PATENT TRADEMARK OFFICE

Address

City

State

Zip Code

Country

Telephone

Fax

Name (Print/Type)

Mark Pahl

Registration No. (Attorney/Agent)

35,325

Signature

[Signature]

Date

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231.

Hair Loss Prevention

By W. Roy Knowles, M.D.

BACKGROUND

My invention relates to preparations useful for maintaining normal, healthy hair bulb function, for preventing hair loss, and for medically treating androgenic alopecia and like dermatological diseases. I will first review pertinent hair biology, then discuss prior art teachings in the field, and then describe my invention.

Hair Biology

Hair bulbs are responsible for normal, healthy hair growth and retention. Hair bulbs are located in the skin, about 3/16 of an inch below the skin surface. They are located just above the fatty layer at the very lower most position of the skin.

The majority of facial and body hair growth is stimulated by androgens. However, the growth of scalp hair has been shown, in genetically programmed individuals, to be inhibited by 5 α -dihydrotestosterone ("DHT") in individuals who exhibit a hereditary pre-disposition to baldness.

Ebling, Dermatol. Clin. S. 467 (1987); Lucky, 4 Biochem. Soc. Transc. 597 (1988); Brodland et al., 47 Cutis 173 (1991).

DHT is produced by reducing testosterone with a 5 α -reductase

enzyme. The phenotypic expression of baldness does not occur in the absence of testosterone. Androgenic alopecia or common baldness represents 99 percent of all cases of hair loss. Broadland, id.

5 The mechanism through which androgens regulate the biology of hair is by modulating the hair growth cycle. Ebling, 4 Biochem. Soc. Trans. 597; Bergfield et al., 5 Dermatol. Clin. 491. The effect of DHT on hair growth appears to be related to local rather than systemic levels of the hormone. This is because the capacity of scalp skin from balding individuals to convert testosterone ("T") to DHT is greater than that observed in the scalp of non-balding individuals. Lucky, *supra*; Schweikert et al., 38 J. Clin. Endocrinol. Metab. 811.

10
15 To prevent hair loss, maintain the health of hair bulbs, or to treat baldness, several compositions are known in the art. We discuss them now.

Hair Loss Prevention

20 Hair loss prevention preparations are known in the art. These include natural product preparations, biological products, vascular toners and testosterone blockers. Several prior art compositions are discussed in the accompanying

Petition To Make Special and its accompanying references, the contents of which are incorporated herein by reference.

Natural Products. Several inventors disclose natural compositions. Casero, United States Letter Patent No. 5,340,579, discloses a composition comprising (a) mucopolysaccharides, (b) human umbilical cord extract, (c) tetrahydrofurfuryl nicotinate, and (d) pharmaceutically and cosmetically acceptable excipients. Buck, United States Letter Patent No. 5,512,275 and 5,609,858, discloses a formulation for the treatment of androgenic alopecia, comprising liquor carbonis detergens in combination with spirits of camphor, castor oil, isopropyl alcohol. Chizick et al., United States Letter Patent No. 5,972,345, discloses a combination of saw palmetto extract, African pygeum extract, and stinging nettle extract.

Biological Products. Hoke, United States Letter Patent No. 5,994,319, discloses using genetic material as a anti alopecia therapeutic. Hoke proposes using anti-sense oligonucleotides targeting 5- α reductases in conjunction with other hair growth enhancers. Tien, United States Letter Patent No. 5,574,011, discloses the use of a class of LHRH analogs for treating male pattern baldness. Messenger, United States Letter Patent No. 6,020,327, discloses administering aromatase inhibitors to treat hair loss. Liao

et al., United States Letter Patent No. 5,422,371 and 5,605,929, discloses a class of anti-androgenic compounds.

Vascular Toners. Several organic chemicals are known to affect the hair growth and hair retention cycle.

5 These include minoxidil. I refer to minoxidil and similar kinds of compounds as "vascular toners," because they are believed to be effective due to their impact on local blood circulation.

10 Minoxidil has been shown to stimulate hair growth or inhibit the loss of hair in a number of patients beginning to develop androgenic alopecia. Minoxidil is the generic name for 6-(1-piperidinyl)-2, 4-pyrimidinediamine 3-oxide. Its preparation is disclosed in Anthony, W.C. et al., United States Letters Patent No. 3,382,247 (1968); McCall, J.M., et
15 al., 40 J. Organic Chem. 3304 (1975); Gorecki, D.K.J., 17 Analytical Profiles of Drug Substances 185 (Academic Press, New York 1988). It is more soluble (by weight minoxidil / volume of solvent) in non-polar solvents than polar ones (75 mg/ml in propylene glycol; 44 mg/ml in methanol; 6.5 in
20 dimethyl sulfoxide; 2.2 mg/ml water).

Minoxidil is medically classified as an anti-hypertensive. It affects heart rate and rhythm. It has thus been used in an oral formulation as a cardiac drug.

Andersson, O., 205 Acta Med. Scand. 213 (1979); Moser, M., 26

Advan. Cardiol. 38 (1979). Over dosage may create cardiac
arrhythmias or other adverse side effects. See e.g.,
Carlson, E.S., 39 Toxicol. Applied Pharmacol. 1 (1977).

5 Minoxidil is also medically classified as an anti-
alopecia agent. Its efficacy in treating early male pattern
baldness has been described in numerous published articles.
E.g., Olsen, E.A. et al., 13 J. Am. Acad. Dermatol. 185
(1985); Novak, E., 24 Int. J. Dermatol. 82 (1982). Its
limited percutaneous absorption and secretion is described in
10 Franz, J.T., 121 Arch. Dermatol. 203 (1985).

The mechanism by which minoxidil alters the hair
growth cycle is uncertain. It is thought to act by
increasing vascular circulation to the hair follicle. It is
known that minoxidil effectiveness is more pronounced in
15 scalp areas which are more vascular.

Topical minoxidil is know to have certain
shortcomings. It is effective in only about eight percent of
adult male users. It produces "lanugo," or baby-type, hair
which is relatively thin. Further, and perhaps most
20 significantly, after approximately 30 months of continuous
use, minoxidil shows a sharp drop in effectiveness. After
about thirty months of use, about half of the new hair growth
falls out. Thus, while the user has somewhat more hair than
originally, the user has less hair than originally seen.

Testosterone Inhibitors. Inhibitors of steroid metabolism, particularly those that inhibit the conversion of testosterone to dihydro testosterone, have shown effects on hair cycles, including inhibition of hair loss. One class of enzymes targeted by these inhibitors are the steroid 5- α reductases.

Certain 5 α -reductase inhibitors have been shown to inhibit hair loss. For example, stump-tail macaque monkeys treated with the 5 α -reductase inhibitor 17b-N,N,-dimethylcarbamoyl- 4-methyl- 4-aza- 5a-androstan- 3-one undergo significantly less age related hair loss than untreated monkeys. Rittmaster et al., 65 J. Clin. Endocrinol. Metab. 188 (1987). Similarly, finasteride, a 5 α -reductase inhibitor, miniaturizes scalp hair follicles, reversing the balding process. "Merck's Propecia Shows Promise In Hair Loss," Marketletter (Mar. 31, 1997). These inhibitors are thought to work by inhibiting the reduction of testosterone to DHT, as DHT is considered to be the more active form. The use of a combination of finasteride and minoxidil demonstrated that, in combination, these two drugs increased the rate of hair growth when compared to either compound administered alone. Diani, 74 J. Clin. Endocrinol. Metabol. 345.

Minoxidil used in conjunction with effectors of steroid metabolism, leads to enhanced hair growth and decreased rates of hair loss.

5 Testosterone blockers are known in the art (I use the term "testosterone blocker" to denote a competitive antiandrogen which inhibits the binding of testosterone or DHT onto its cell surface binding site, rather than a compound which is used to inhibit the reduction of testosterone into DHT.). Also known is their use
10 systemically (orally or intravenously). As systemic therapeutics, they are known in the art as having a key shortfall: their long term efficacy is compromised by their blocking of the androgenic feedback inhibition of gonadotropin secretion. This interference results in
15 elevated gonadotropin secretion, which in turn increases testicular secretion of testosterone. The higher level of testosterone eventually overcomes the action of the antiandrogen. Liao, *supra*, at col. 3, lines 16-31.

20 Thus, what is needed in the art is a safe and effective way to maintain both the healthy function of hair bulbs, and the health of existing hair, that avoids the shortfalls seen in the prior art.

SUMMARY

I have invented a kind of hair loss prevention composition. My invention is a new combination of already known types of compounds. My invention can be used either
5 cosmetically (to maintain healthy hair growth) or pharmaceutically (to treat a medical condition). It can be made using components already known in the art, allowing one to enjoy the predictability of use available with these old compounds. My invention is flexible enough, however, to also
10 allow one to substitute newly-discovered compounds substantially equivalent to the already known compounds. Thus, my invention can be adapted to allow the user to use the safest, most effective components then available.

I have found that certain compounds have greatly
15 improved effectiveness - achieving *ten times* the benefit, or an entire order of magnitude - if combined with a skin penetration enhancer. The penetration enhancer delivers these compounds to the hair bulb, where the compounds are most needed.

20 I have thus found that testosterone blockers, if applied topically (rather than systemically administered), are effective in preventing hair loss, and if used in conjunction with a dermal penetration enhancer. Such topical use avoids precipitating the systemic increase in

testosterone production seen with oral administration, by
minimizing systemic interference with normal gonadotropin
secretion. I have also found that vascular toners, if
applied topically in conjunction with a dermal penetration
enhancer, work much better.

DETAILED DESCRIPTION

My invention includes a skin penetration enhancer
used together with a testosterone blocker or a vascular
enhancer, or both. I first discuss each component
individually, and then discuss the combinations of these
components that I have found most acceptable.

Penetration Enhancers

You can use a variety of skin penetration enhancers
to make compositions that work as I intend. Penetration
enhancers and skin penetrating formulations are known in the
art. These include the variety of formulations used from
time to time for both psoriasis treatment pharmaceuticals,
and psoriasis prevention nutritional supplements and
cosmetics.

The penetration enhancer (or penetration agent)
should be accepted for human use by relevant government
agencies. Thus, dimethyl sulfoxide, while within the scope
of the claims, is not a preferred penetration enhancer where

that compound is not approved for human topical use. The penetration enhancer should not chemically react with any other ingredient to impair or alter the composition's stability and shelf life. Thus, one should examine the possible reactivity of a given penetration enhancer with a given testosterone blocker or vascular toner.

The penetration agent should be cosmetically acceptable. Thus, while I have tested dimethyl acetate, I do not favor it. While it is within the scope of the claims, it is a weak penetration enhancer. Thus, one needs to use a lot of it. In these high amounts, it smells bad. In contrast, methyl acetate is odorless, and I have tested and found it acceptable.

Several inventors disclose liposome technology to deliver cosmetic and dermatology materials. See, for example, Lishko et al., United States Letter Patent No. 5,753,263, discloses using liposomes to selectively deliver a composition to hair follicles. Liposomes are made of fatty material, and are suitable for delivering homogenous types of materials. As such, it may be difficult for a liposome to in fact work with a combination of a polar compound (like a minoxidil vascular toner) and a non-polar compound (such as a progesterone testosterone blocker). I thus do not consider

liposome technology within the scope of the term "penetration enhancer" in this patent.

Vascular Toners

My invention works with a variety of vascular
5 toners. One can make compositions within the scope of my
invention with minoxidil analogs or derivatives, or with
other anti-alopecia agents, such as diphencyprone, which work
in a similar way, by improving local blood flow to the
affected hair bulbs. Because it has such a broad volume of
10 use and scientific study, I prefer to use minoxidil. I thus
use it as an example throughout this specification.

A vascular toner, if used to maintain healthy
function of hair bulbs, must be delivered to the small blood
vessels feeding the hair bulbs. I have thus found that the
15 effectiveness of the vascular toner is greatly improved if it
is topically applied along with a penetration enhancer. This
allows the vascular toner to act locally.

The vascular toner must be carefully titrated
against the penetration enhancer. For example, for a given
20 concentration of minoxidil, one needs to use the penetration
enhancer in the appropriate concentration. If a given
penetration enhancer is used in a too high concentration, the
minoxidil may penetrate through the skin and reach the
systemic blood circulation. It can there, if present in

sufficient amount, cause side effects as seen by taking oral minoxidil. Thus, it is necessary to adjust the amounts of penetration enhancer and vascular toner, depending on the concentration and specific identity of the enhancer and the toner.

Adding a penetration enhancer to the vascular toner appears to fundamentally change the biological mechanism by which the vascular toner works. This is shown by the qualitatively different results seen between minoxidil and my compounds. The two products produce different types of hair, and for different time periods.

Minoxidil without a penetration enhancer (as available in ROGAINE™ topical minoxidil U.S.P.) produces a different kind of hair than does minoxidil used with a penetration enhancer. It is known in the art that topical minoxidil without a penetration enhancer (as is commercially available in ROGAINE (TM) topical minoxidil U.S.P., commercially available from Pharmacia & Upjohn Inc., Bridgewater, New Jersey) results in thin, baby-like, temporary hair, called "lanugo" hair. I have found that my compounds, by contrast, result in good, coarse, "terminal" hair, hair which is normal, permanent adult hair.

This indicates that minoxidil without and with penetration enhancer may act on different types of hair

bulbs, or produce different responses from the same hair
bulbs. Minoxidil without enhancer is only weakly soluble in
polar solvents. See supra. It thus has difficulty diffusing
to the deeply located hair bulbs (roots) which are located
just above the deep fat layer. Minoxidil without enhancer
may thus affect only hair bulbs located close to the skin
surface, or located in a less fatty skin layer, or hair bulbs
most sensitive to changes in blood flow. Alternatively, it
may affect the same hair bulbs, but with such weak or
attenuated effect that the hair bulbs produce a different
type of hair.

In contrast, my compounds produce normal, terminal
hair. This indicates that my compounds act directly on the
mature, adult hair bulbs responsible for terminal hair
growth.

Further, it is known in the art that minoxidil
users experience a sudden drop in hair thickness after about
thirty months of usage. I thus have sought the time at which
my compounds have a sudden drop in effectiveness.

Surprisingly, I have found that my compounds apparently do
not lose effectiveness at all, even after using them for
substantially greater than thirty months. This confirms that
while my compounds appear to simply restore or preserve
normal hair bulb function, the prior art compositions do not

restore normal hair bulb function, but actually provoke an abnormal function - the growth by an adult of baby like, temporary hair. That this function is abnormal is confirmed by its drop in effectiveness after thirty months; such a drop in efficacy indicates a "tolerance" acquired against the intervention, rather than the maintenance of a permanent, healthy state.

This indicates that the physiological mechanisms and biomedical pathways of the two preparations are different. Minoxidil alone, in the concentrations typically used, may actually temporarily alter a normal adult body function (causing the adult body to temporarily produce infant hair). In contrast, my invention simply maintains the normal function of the healthy adult body hair bulb, allowing it to continue to produce normal adult hair as long as the compound is used.

I have also found that the effect of the formulations depends on location of administration. Using the specific formulations disclosed here, I have observed decreases in hair loss, and a consequent statistically significant increase in the amount of healthy mature hair, after 4.0 - 4.5 months on the frontal scalp. On the crown and back of the head, by contrast, I have observed statistically significant results after 4.5 - 5.0 months.

The frontal scalp may react faster because it enjoys greater vascularization and blood flow than the other parts of the scalp.

5 Testosterone Blocker

My invention works with a variety of testosterone blockers. I prefer to use a blocker already approved for human use by the United States Food & Drug Administration, as these types of testosterone blockers, if used in pharmaceutical (as opposed to cosmetic) versions of my invention, do not need to undergo as lengthy and expensive a process to verify their safety and efficacy as used in pharmaceutical products. Examples include flutamide, cyproterone acetate, spironolactone, progesterone, or analogs or derivatives of any of these (e.g., 17-hydroxy-16-methylene- Δ^6 -progesterone, 17 α -hydroxyprogesterone).

I have found several surprising things about testosterone blockers. First, they are not actually necessary for my invention to work; minoxidil alone is effective on 8% of patients, while the same amount of minoxidil administered with the proper amount of a penetration enhancer is effective on 35% of patients. Second, testosterone blockers added to such a mix are

synergistically beneficial, increasing the efficacy from 35% to 85% of patients.

One testosterone blocker is the anti alopecia compound cioteronel. Cioteronel is the common name for
5 hexahydro-4-(5-methoxyheptyl)-2(1H)-pentalenone. It is also known, or is commercially available, as X-ANDRON™, CPC-10997, CYOCTOL™, and EXANDRON™. It is a clear, colorless oil, soluble in lipid and relatively non-polar solvents. Its preparation is disclosed in Kasha, W.J., PCT Int'l Patent Application
10 83/04,019 (1983), 101 Chem. Abstr. 23037k (1984). Its use is disclosed in United States Letter Patent No. 4,689,345. Its inhibition of DHT binding in vitro is disclosed in Rec. Adv. Chemotherapy (Proc. 14th Int'l Congr. Chemotherapy Antimicrob., Sect. 1) at 261-70 and 273-74
15 (Univ. Tokyo Press, 1985). Its cutaneous metabolism and clinical pharmacokinetics is disclosed in de Zeeuw et al., 7 Pharm. Res. 638 (1990), Weichers et al., 65 Int. J. Pharm. 77 (1990).

Another testosterone blocker is progesterone,
20 pregn-4-ene-3, 20-dione (commercially available as CORLUTINA™, CORLUVITE™, CYCLOGETS™, GESTIRON™, GESTONE™, LIPOLUTIN™, LUTOCYCLIN M™, PROGESTIN™, CP progesterone powder, etc . . .). Progesterone is insoluble in water and soluble in alcohol, acetone, dioxane, and concentrated

sulfuric acid. It is sparingly soluble in vegetable oils. Its isolation, structure and biological activity is described at length in Bardin et al. (eds.), Progesterone and Progestins (Raven Press, New York 1982). I prefer to use
5 progesterone as the sole testosterone blocker.

Carrier Vehicles

The penetration enhancer and the vascular toner or testosterone blocker, or both, may be mixed with a carrier
10 vehicle. You can use a variety of vehicles to make my invention. The vehicle is simply a cosmetically safe, medically safe solvent for the active ingredients. The vehicle should not adversely and significantly chemically react with the active ingredients.

15 For example, propylene glycol, water and isopropyl alcohol may be used as vehicles. These may be used alone or in combination.

20 The vehicle can optionally provide functions in addition to simply dissolving the active ingredients. For example, one can use a moisturizing vehicle, or a vehicle containing sunscreen. For a moisturizing or moisture retaining vehicle, one can use a vehicle made from a combination of (ranked in order of quantity used) water, mineral oil, petrolatum, lanolin, sorbitol solution, stearic

acid, lanolin alcohol, cetyl alcohol, glyceryl stearate /
PEG-100 stearate, triethanolamine, dimethicone, propylene
glycol, tri(PPG-3 myristyl ether) citrate, disodium EDTA,
methylparaben, ethylparaben, propylparaben, fragrance,
5 xanthan gum, butylparaben, and methyldibromo glutaronitrile.

It may be desirable to use a vehicle containing one
or more sunscreens. This is because my preparations are used
on the tops of balding scalps. Balding scalps are often
largely unprotected from sun damage, as the user may not wear
10 headgear and the balding scalp lacks the sun shielding dense
hair layer present on a healthy scalp. Adding sunscreen thus
can protect the scalp from possible sun damage. Sunscreens,
and vehicles containing sunscreen compounds, are widely known
in the art. See, e.g., United States Letter Patent No.
15 4,522,807.

Other cosmetic vehicles are widely known in the
art. I prefer to use VEHICLE/NTM as the vehicle. I prefer to
use VEHICLE/N (TM) because it has a cosmetically attractive
"feel" to the user. Vehicle/N (TM) is commercially available
20 from the Neutrogena Dermatologics division of Johnson &
Johnson, Inc., New Brunswick, New Jersey. It is currently
available in two formulations, regular and mild. They are
both versatile liquid vehicles for extemporaneous compounding
of topical drugs. Both formulations solublize selected

dermatological agents and provide astringent and drying actions.

The VEHICLE/N (TM) ingredients are SD alcohol 40 (45%), purified water (<45%), laureth-4 (>4%), isopropyl alcohol (4%) and propylene glycol (<4%). The VEHICLE/N (TM) mild ingredients are purified water (>37.5%), SD alcohol-40 (37.5%), isopropyl alcohol (5%) and laureth-4 (<5%). To compound with VEHICLE/N, add the appropriate quantity of active ingredient to yield the intended concentration.

VEHICLE/N (TM) is available as 50 mL of vehicle in a plastic bottle with applicator top. The bottle is filled only to 3/4 capacity, to ensure proper mixing. For 50 mL of VEHICLE/N, use the following amounts:

Desired Concentration	0.1%	0.2%	0.5%	1.0%
Bulk Active	50 mg	100 mg	250 mg	500 mg
Tablets			1x250mg	4x150 mg 1.2% soln
Desired Concentration	2.0%	3.0%	4.0%	5.0%
Bulk Active	1.0 gm	1.5 gm	2.0 gm	2.5 gm

For fastest dissolution, when tablets are used, crush them to a powder and then add the powder to the vehicle. When capsules are used, add the capsule contents only to the vehicle, and discard the capsule shell. Shake the mixture

gently. Most capsule contents and bulk active ingredients will dissolve within minutes, though some may take longer.

VEHICLE/N™ is available in a bottle with an APPLIDERM (TM) applicator top. The APPLIDERM (TM) applicator unit automatically filters the compounded mixture and provides a convenient, spill-proof, self-contained unit for topical application. To use the APPLIDERM (TM) applicator unit, push the applicator firmly into the bottle using the white cap as a holder. Screw the cap all the way down to seat the applicator. Shake well. If tablets are dissolved in the vehicle, then the user should be instructed to allow the solution to stand overnight and to shake vigorously before the first use. VEHICLE/N (TM) should not be used near fire or open flame due to alcohol content. Both VEHICLE/N (TM) and VEHICLE/N (TM) mild contain substantial alcohol and are not suitable for use in acute dermatoses. Stinging may be noted if used on irritated or abraded skin. Avoid contact with eyes or eyelids. If the product accidentally comes in contact with eyes, rinse thoroughly with water and contact physician. Keep out of reach of children. VEHICLE/N (TM) and VEHICLE/N (TM) mild are contraindicated in persons who have shown hypersensitivity to any of the listed ingredients.

Preferred Formulations

Given a constant amount of testosterone blocker or vascular toner, I have found that lower concentrations of penetration enhancer can decrease the efficacy of the final formulation, while higher concentrations of penetration enhancer increase the risk of adverse side effects due to systemic penetration of the other active ingredient(s).

Similarly, you may use different testosterone blockers for the same effect, and may use more or less of it. Using more testosterone blocker allows one to use relatively less penetration enhancer, or a weaker enhancer. Titration of the two components against one another is a conventional technique well known in the art of pharmaceutical and cosmetics formulation. Such techniques are already used to titrate formulations for the wide variety of trans-dermal drugs and cosmetics currently available.

For example, in a four ounce quantity of liquid containing 5 drops of trimethyl acetate, I prefer to use one percent (by volume) of soluble progesterone (U.S.P.).

A preferred formulation is:

Minoxidil	1.0 gm bulk powder
Soluble progesterone (U.S.P.)	0.5 gm
Trimethyl acetate	5 drops
Vehicle N (TM)	50 mL

The following preparation is acceptable, and within the scope of the claims, but I do not prefer it:

Minoxidil	1.0 gm bulk powder
Soluble progesterone (U.S.P.)	0.5 gm
Methyl acetate	5 drops
Vehicle N (TM)	50 mL

5

Alternatively, an ethyl alcohol - water - propylene glycol solution may be used as the diluents and vehicle. For 100 mL of this formulation, use:

ethyl alcohol 95%	75.5 cc
purified water	18.5 cc
propylene glycol	6.0 cc
progesterone	1.5 gm
minoxidil	2.0 - 5.0 gm
methyl acetate	5.0 gtts

10

These are my preferred formulations. These may be varied as desired, but it is necessary to watch for unwanted side effects possibly due to unwanted systemic penetration of the active ingredient(s). For example, minoxidil is pharmaceutically and cosmetically effective topically at

anywhere from about 0.01 grams to about 50 grams per four ounces, depending on the frequency of topical administration. Testosterone blockers are also pharmaceutically and cosmetically effective topically at anywhere from about 0.01 grams to about 50 grams per four ounces, depending on the frequency of topical administration. With the higher concentrations, however, increasing the amount of penetration enhancer creates a greater risk of adverse side effects.

Summary

I have discussed several different specific formulas. I have found these most useful. One can, however, vary the constituents to achieve the same effect without having a substantially different product. For example, one can use a different testosterone blocker, or a weaker penetration enhancer in a higher concentration. Thus, the legal scope of my patent is not limited to the specific examples I discuss herein; rather, the legal coverage of this patent is defined by the appended claims and their equivalents.

CLAIMS

1. A composition of matter intended for topical use in preventing or treating alopecia, or maintaining healthy hair, said composition of matter comprising:

- 5 a) an active compound selected from the group consisting of: a pharmaceutically or cosmetically effective topical amount of a testosterone blocker and minoxidil, and
- 10 b) a penetration enhancer, said penetration enhancer present in a concentration sufficient to aid said active compound in penetrating the skin surface to a depth of approximately the depth of hair bulbs.

15 2. The composition of claim 1, wherein said active compound comprises a testosterone blocker.

 3. The composition of claim 1, wherein said active compound comprises minoxidil.

 4. The composition of claim 3, further comprising a testosterone blocker.

20 5. The composition of claim 4, wherein the ratio of penetration enhancer to testosterone blocker to minoxidil in the composition is approximately 5 drops : 0.5 grams : 1 gram.

6. The composition of claim 4, wherein said penetration enhancer is trimethyl acetate and wherein said testosterone blocker is progesterone.
7. The composition of claim 5, wherein said testosterone blocker is present in a concentration of 0.5 grams per 4 ounces of finished liquid.
8. The composition of claim 4, labeled for topical cosmetic use in maintaining normal, healthy hair.
9. The composition of claim 4, labeled for topical pharmaceutical use in preventing or treating a disease.
10. The composition of claim 9, wherein said disease comprises alopecia.
11. The composition of claim 4, further comprising a sunscreen in an amount effective to screen radiation.
12. A for preventing or treating alopecia, or maintaining healthy hair, said method comprising:
 - a) Topically administering an active compound selected from the group consisting of: a pharmaceutically or cosmetically effective topical amount of a testosterone blocker and minoxidil, together with
 - b) a penetration enhancer, said penetration enhancer present in a concentration sufficient to aid said active compound in penetrating the

skin surface to a depth of approximately the
depth of hair bulbs.

13. The method of claim 12, wherein said active compound
comprises a testosterone blocker.

5 14. The method of claim 12, wherein said active compound
comprises minoxidil.

15. The method of claim 14, wherein said active compound
further comprises a testosterone blocker.

10 16. The method of claim 15, wherein the ratio of
penetration enhancer to testosterone blocker to
minoxidil in the composition is approximately 5 drops :
0.5 grams : 1 gram.

15 17. The method of claim 15, wherein said penetration
enhancer is trimethyl acetate and wherein said
testosterone blocker is progesterone.

18. The method of claim 16, wherein said testosterone
blocker is present in a concentration of 0.5 grams per 4
ounces of finished liquid.

20 19. The method of claim 15, labeled for topical cosmetic
use in maintaining normal, healthy hair.

20. The method of claim 15, labeled for topical
pharmaceutical use in preventing or treating a disease.

21. The method of claim 20, wherein said disease comprises
alopecia.

22. The method of claim 15, further comprising a sunscreen
in an amount effective to screen radiation.

ABSTRACT

Compositions to prevent or reduce hair loss,
allowing the body to maintain normal, healthy hair growth,
comprising a penetration enhancer together with a
5 testosterone blocker or a vascular enhancer, or both.

X:\PohlM\Knowles\Specif2.Doc

Please type a plus sign (+) inside this box → ☐

PTO/SB/01 (12-97)

Approved for use through 9/30/00. OMB 0651-0032

Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

**DECLARATION FOR UTILITY OR
DESIGN
PATENT APPLICATION
(37 CFR 1.63)**

☒ Declaration
Submitted with Initial
Filing OR ☐ Declaration
Submitted after Initial
Filing (surcharge
(37 CFR 1.16 (e))
required)

Attorney Docket Number	Knowles/Hair Loss
First Named Inventor	Knowles
COMPLETE IF KNOWN	
Application Number	/
Filing Date	
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Hair Loss Prevention

the specification of which (Title of the Invention)

☒ is attached hereto
OR

☐ was filed on (MM/DD/YYYY) as United States Application Number or PCT International

Application Number and was amended on (MM/DD/YYYY) (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached?	
				YES	NO
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	<input type="checkbox"/> Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

[Page 1 of 2]

Burden Hour Statement: This form is estimated to take 0.4 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

Please type a plus sign (+) inside this box → ☐

PTO/SB/01 (12-97)
Approved for use through 9/30/00. OMB 0651-0032
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☒ Customer Number ☐ OR ☐ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number
			22925
			PATENT TRADEMARK OFFICE

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☒ Customer Number ☐ OR ☐ Correspondence address below

Name					
Address					
Address					
City		State		ZIP	
Country		Telephone		Fax	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor:		<input type="checkbox"/> A petition has been filed for this unsigned inventor			
Given Name (first and middle (if any))		Family Name or Surname			
W. Roy		KNOWLES			
Inventor's Signature	W. Roy Knowles MD			Date	7-13-00
Residence: City	HOUSTON	State	TX	Country	USA
Post Office Address	7500 San Felipe, Suite 850 850				
Post Office Address					
City	Houston	State	TX	ZIP	77003
				Country	USA

☐ Additional inventors are being named on the _____ supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto